Combining Early Coagulation and Inflammatory Status Improves Prediction of Mortality in Burned and Nonburned Trauma Patients

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Background: **After injury, there is a synergistic response between inflammation and coagulation systems. We hypothesized that combining markers of these processes and standard clinical indices would improve early prediction of in-hospital mortality in burned and nonburned trauma patients.**

Methods: **Patients admitted to the surgical or burn intensive care unit within 24 hours of injury with an anticipated stay ≥3 days were enrolled during a one year period. Upon admission, blood was drawn for thromboelastography, plasma-based clotting assays, and cytokine levels. Clinical indices and multiple organ dysfunction syndrome (MODS) scores were recorded. Candidate variables evaluated included age, percentage third degree burns, inhalation injury, percentage total body surface area burns, interleukin-6, tumor necrosis factor alpha, interleukin-8, prothrombin time, partial thromboplastin time (PTT), maximal amplitude reflective of clot strength, group (burn or nonburn) and admission MODS. Multiple logistic regression with stepwise selection and likelihood ratio test was performed to identify predictors for mortality. A receiver operating characteristic (ROC) curve was constructed to assess the diagnostic performance of identified predictors. Validation of the model with an additional cohort was performed.**

Results: **For model development, we enrolled 25 burned and 33 nonburned trauma patients (20 blunt and 13 penetrating injuries). Fifteen deaths occurred. Multiple logistic regression analysis identified six independent risk factors for death: age, percentage third degree burns, inhalation injury, tumor necrosis factor alpha level, maximal amplitude, and MODS score with an area under ROC curve of 0.961 (95% confidence interval: 0.891, 1.000, $p < 0.05$). The area under the ROC curve for the validation cohort (n = 66) was 0.936 (95% confidence interval: 0.875, 0.997, $p < 0.001$).**

Conclusion: **Our model improves prediction of in-hospital mortality in comparison to previous methods for burn and nonburn trauma patients. Furthermore, our model is equally applicable to all patients regardless of type of traumatic injury (nonburn or burn). This improvement is because of the inclusion of patient's early coagulation and inflammatory status in addition to standard clinical indices. These data provide a baseline within which to measure incremental improvements in care.**

Key Words: **Thromboelastography, Cytokine, Third degree burns, Inhalation injury, Tumor necrosis factor, Multiple organ dysfunction syndrome.**

J Trauma. 2008;64:S188–S194.

Prognostic scoring systems allow comparisons of quality of care by objectifying and standardizing indicators of illness severity. They also facilitate patient stratification in research or treatment protocols and allow a clinician to distinguish between the effects of treatment and the effects of disease. Several different prediction models for multiple organ failure are currently used as markers of mortality, but there is no consensus as to which multiple organ dysfunction model or scoring system is best. We hypothesized that combining the early indicators of a patient's coagulation and inflammatory status in addition to standard clinical indices would improve early prediction of in-hospital mortality in burned and nonburned trauma patients.

The rationale for adding coagulation and inflammatory parameters to a prognostic scoring system rises from the growing body of research pointing to their interrelationship.[1–4] After injury, there is a synergistic response between inflammation and coagulation systems. Initiators of inflammation, such as trauma or burns, instigate a cascade of intracellular events within monocytes. This ultimately causes synthesis of cytokines such as tumor necrosis factor alpha (TNF), interleukin-1 (IL-1), IL-6, and IL-8.[5,6] Cytokines injure endothelium by activating and amplifying the numbers of neutrophils, platelets, and monocytes. These cytokines then activate the coagulation cascade by increasing the expression of tissue factor (TF) from the perivascular cells, endothelium, and monocytes.[7] Furthermore, cytokines disrupt the capillary

Submitted for publication October 30, 2007.

Accepted for publication October 30, 2007.

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Supported by the US Army Medical Research and Medical Command. The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense (AR 360-5).

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DOI: 10.1097/TA.0b013e318160a5a3

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Report Documentation Page

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1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
OCT 2007		**00-00-2007 to 00-00-2007**

4. TITLE AND SUBTITLE	5a. CONTRACT NUMBER
Combining Early Coagulation and Inflammatory Status Improves Prediction of Mortality in Burned and Nonburned Trauma Patients	5b. GRANT NUMBER
	5c. PROGRAM ELEMENT NUMBER
6. AUTHOR(S)	5d. PROJECT NUMBER
	5e. TASK NUMBER
	5f. WORK UNIT NUMBER
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) **U.S. Army Institute of Surgical Research (USAISR),3400 Rawley E. Chambers Avenue,Fort Sam Houston ,TX,78234-6315**	8. PERFORMING ORGANIZATION REPORT NUMBER
9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)	10. SPONSOR/MONITOR'S ACRONYM(S)
	11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION/AVAILABILITY STATEMENT
Approved for public release; distribution unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

15. SUBJECT TERMS

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			
unclassified	**unclassified**	**unclassified**	**Same as Report (SAR)**	**7**	

membranes and contribute to organ damage. This is consistent with reports of prominent extravascular coagulation and fibrin deposition in the alveolar compartments of patients with acute respiratory distress syndrome (ARDS), which is the most common organ failure in multiple organ dysfunction syndrome (MODS).[8,9]

Conversely, coagulation can also initiate inflammation. In vitro studies measuring cytokine levels after culture of coagulated whole blood were significant for elevated levels of IL-6 and IL-8. Furthermore, the addition of hirudin or TF pathway inhibitor attenuated this response.[10] It has been shown that the binding of thrombin to its receptor initiates NF-kB-dependent inflammatory gene transcription in the endothelium and TF can initiate gene expression of proinflammatory cytokines in monocytes.[2,11,12]

The predictor models for critically ill patients often cited in the literature are the Logistic Organ Dysfunction (LOD) score,[13] the MODS,[4] and the Sequential Organ Failure Assessment (SOFA) score[14] and the multiple organ failure (MOF) model for trauma patients by Sauaia and colleagues.[15] The LOD score takes into account the importance of the organ system relative to the others as well as the degree of severity within that system. The MODS was derived from a systematic literature review followed by a prospective cohort study that led to a scoring system incorporating six organ system dysfunctions. The SOFA score allows a clinician to track a patient's organ dysfunction during the intensive care unit (ICU) stay and is a marker of morbidity. The MOF model by Sauaia can be used to predict multiple organ failure as early as 12 hours after injury. All of these systems incorporate clinical and laboratory parameters to derive a score.

However, with the exception of the LOD score, which includes changes in prothrombin time (PT), the published scoring systems, such as the Acute Physiology and Chronic Health Evaluation (APACHE) III, Simplified Acute Physiology Score (SAPS II), the Mortality Probability Model (MPM), and those mentioned above do not account for coagulopathy. Additionally, none of these models include a variable reflective of postinjury inflammation.[4,13,14,16] In this study, we investigated whether a patient's coagulation and inflammatory status at the time of ICU admission helps predict in-hospital mortality. This is the first prognostic scoring system that incorporates both of these parameters.

METHODS

This study was approved by the Institutional Review Board. All severely burned and trauma patients with or without inhalation injury admitted to the ICU were considered for enrollment. Patients had to be 18 years or older, admitted within 24 hours of injury, and have an anticipated stay of 72 hours or greater in the US Army Institute of Surgical Research, and those who presented more than 24 hours after injury.

Blood Sample Collection

Baseline blood specimens were collected from each subject within 24 hours of admission. Samples of 20 mL were taken from arterial or central lines inserted for standard clinical care. If the central line was used for sampling, the first 5 mL of blood withdrawn was discarded before 20 mL was drawn for the study. Blood sampling was stopped when a patient was transferred from the ICU or the arterial and central lines were discontinued. A one-time blood draw was also performed on 20 healthy volunteers for control samples.

Sample Processing

The blood sample was divided between three 4.5 mL tubes containing citrate, a 3.5 mL ethylenediaminetetraacetic acid (EDTA) tube, and 3 mL for thromboelastography (TEG) analysis. The three 4.5 mL citrate tubes were centrifuged at 1,000*g*/3,500 revolutions per minute for 15 minutes. The supernatant from these tubes was then placed into a 4.6 mL cryoprecipitate tube for later coagulation and cytokine analysis. All cryoprecipitate tubes were stored at -70°C until assayed. All plasma clotting analysis was performed in an onsite laboratory. The complete blood count was performed using the blood in the EDTA tube.

Plasma Based Clotting Assays

Samples were thawed in a 37°C water bath for 10 minutes. PT, PTT, fibrinogen, and D-dimers were measured by BCS Coagulation Analyzer (Dade Behring, Deerfield, IL) following the manufacturer's protocols.

Cytokine Analysis

Cytokine analysis was performed at Clinical Investigation Division of the Brooke Army Medical Center. The assays for IL-1, IL-6, IL-8, and TNF were performed simultaneously via five multiplexed solid phase direct sandwich immunoassays comprising a human inflammatory five-plex assay kit (Biosource International, Camarillo, CA, Cat # LHC0003) analyzed on a Luminex 100 luminescent analyzer (Luminex, Austin, TX). The Luminex instrument was calibrated daily and all equations used for analysis of the standard curves had r^2 values exceeding 0.99.

Thromboelastography

Quality control checks were completed within 8 hours of blood collection per manufacturer's protocol (Hemoscope, Niles, IL). Before placing the samples into the TEG machine, the machine was set at the patient's current body temperature and 0.10 μL of the TF solution were added to each cup. The TF solution was prepared daily by placing 0.990 mL of saline per 0.01 mL of recombinant human TF (Dade Behring, Deerfield, IL). Within 4 minutes of obtaining the blood sample, 0.35 mL of whole, native blood was added to each cup and the temperature setting was checked for accuracy. The TEG was started and stopped 60 minutes after maximal amplitude

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(MA). In patients who were prescribed heparin for deep vein thrombosis prophylaxis, heparinase cups were used to deactivate this anticoagulant. Duplicate TEGs were performed and the mean calculated.

Each TEG parameter, R, K, α, MA, LY30 and LY60, represents a different aspect of the patient's hemostasis. R measures the time until the onset of clotting; this is the point at which all other plasma coagulation assays stop measuring. Its value will increase if there is a deficiency of coagulation factors. K time is the interval measured from R time to a fixed level of clot firmness, the point at which the amplitude of the tracing reaches 20 mm. α measures the angle between the tangent line drawn from the curve to the split point and the tracing's horizontal line, in degrees. It is affected by the rate of fibrin-platelet interaction. The higher the α angle, the higher the rate of clot formation via this interaction. MA measures the maximum amplitude, the maximal strength of the clot. It is the end-product of maximal platelet-fibrin interaction, which is the end product of coagulation that affords injured tissue from continued hemorrhage. After MA is reached, fibrinolysis ensues. LY30 and LY60 measure the rate of amplitude reduction 30 minutes and 60 minutes after MA, reflective of the state of fibrinolysis of the patient.

Clinical Database

Clinical data were collected and entered into an Oracle database for analysis for each subject in the ICU up to 30 days or until the patient was transferred. All laboratory tests and basic demographic data were imported into the database through a direct interface from patients' medical records. Data entered into the database from daily data collection worksheets and verified by a research nurse included gender, age, injury severity scores (ISS), percentage total body surface area (% TBSA) burns, percentage third degree burns (% FT), presence of inhalation injury (II), surgical procedures performed, list of all injuries, total number of days in ICU, probability of survival in Burns (Burn_PS),[17] probability of survival in nonburn trauma patients using the Trauma Score Injury Severity Score (TRISS),[18] total number of hospital days and outcome (dead or alive). Also, a MODS score was collected using the worst organ system scores as defined by Marshall et al.[4] If the central venous pressure data needed to calculate Marshall's cardiovascular organ dysfunction score was not available, pressor requirement or systolic blood pressure was used as surrogates. Missing data were imputed as zero when calculating MODS scores.[4]

Statistical Method

Data were analyzed with use of SAS version 8.1 (SAS Institute, Cary, NC). Demographic data were expressed as mean ± standard deviation. Univariate analysis was performed with use of two-sample Student *t* test or Wilcoxon Rank Sum test for continuous variable and χ^2 test for categoric variables. Patients who died were compared with those who lived. In addition, Pearson correlation coefficients were calculated to analyze relationships between continuous variables, between dichotomous and continuous variables (called Point-biserial correlation), and between dichotomous variables (Phi).

Multiple logistic regressions with stepwise selection and likelihood ratio test were performed to identify significant predictors for mortality. We chose variables with a p value of less than 0.2 in the univariate analysis as the final candidate variables for the logistic model.[19] Then, we removed those that were highly correlated with others (confounding variables) from the final candidates for the logistic model. Hosmer-Lemeshow goodness-of-fit test was used to estimate the regression model fit. A receiver operating characteristic (ROC) curve was constructed to assess the diagnostic performance of identified predictors in the model development patients (n = 58). The model was independently validated by in an additional cohort of 66 patients.

Additionally, we compared our model's mortality ROC curves of the trauma and burned patients in the validation cohort with 1-TRISS and 1- Burn_PS, respectively.

RESULTS

Model Development

Sixty-one patients were enrolled between April 2004 and May 2005. Data for three patients were removed because of death within 48 hours of injury. The remaining 58 patients were screened for evidence of active hemorrhage at the time of blood draw and were not found to be actively bleeding. We enrolled 33 trauma patients (20 blunt and 13 penetrating) and 25 burned patients (eight with inhalation injury) (Table 1). No patient had combination of burn and nonburn traumatic injuries.

Candidate variables evaluated upon admission to the ICU were age, ISS, % FT, II, % TBSA, MODS score, base deficit, group (burned or nonburned trauma), IL-1, IL-6, TNF, IL-8, PT, PTT, factor 2, fibrinogen, D-dimer, R time, K

Table 1 Demographic Data (Mean ± Standard Deviation)

	Model Cohort (n = 58)	Validation Cohort (n = 66)
Age	47 ± 19	42 ± 19
Gender		
Male	76% (44)	77% (51)
Female	24% (14)	23% (15)
ISS	23 ± 14	26 ± 10
Injury type		
Blunt	34% (20)	51% (34)
Penetrating	22% (13)	11% (7)
Burn	44% (25)	38% (25)
Burn		
2nd Degree	22 ± 17%	13 ± 11%*
3rd Degree	10 ± 15%	24 ± 25%*
Hospital days	31 ± 33	31 ± 31
ICU days	18 ± 23	18 ± 21
Ventilator days	15 ± 20	11 ± 16

* $p < 0.05$.

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time, α-angle, MA, LY30 and LY60. These variables were compared between survivors and nonsurvivors. Those whose $p < 0.2$ were: group (burned vs. nonburned trauma), II, ISS, age, % FT, % TBSA, MODS, base deficit, IL-1, TNF, factor 2, MA, LY30 and LY60. Variables that were collinearly related (group, ISS, TBSA, base deficit, IL-1, factor 2, LY30 and LY60) were eliminated from further analysis. In subsequent multiple logistic regression with stepwise selection, we identified six independent risk factors for death: % FT, II, age, MOD score, TNF, and MA (Table 2). The area under the ROC curve was 0.961 (95% confidence interval [CI]: 0.891, 1.000, $p < 0.05$) for the model with the Hosmer-Lemeshow goodness-of-fit test of 0.72. When TNF and MA were removed from the model (Reduced Model), the area under ROC curve was 0.900 (95% CI: 0.787, 1.000). When only MODS score was used in our patients to predict mortality, the area under ROC curve was even lower with 0.660 (95% CI: 0.500, 0.835) (Fig. 1).

Table 2 Predictors of Mortality Determined by Logistic Regression With Stepwise Selection: in Order of Rank

Predictor	Regression Coefficient	Odds Ratio Point Estimate	95% Wald Confidence Interval
Intercept	–15.6563		
% FT	0.2645	1.303	1.034–1.642
Inhalation injury	–1.6715	0.035	0.001–0.859
Age	0.0818	1.085	0.999–1.179
MODS score	0.5051	1.657	0.979–2.804
TNF (ng/mL)	0.0256	1.026	0.995–1.058
MA (mm)	0.0958	1.101	0.953–1.271

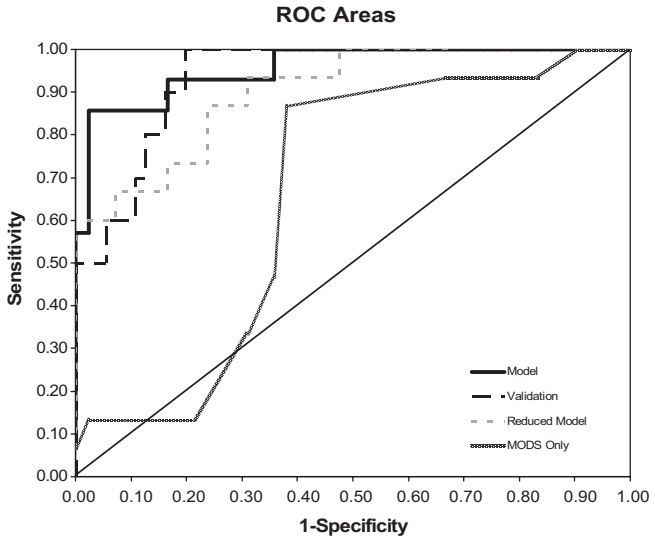

Fig. 1. *ROC curves for the model, reduced model, MODS only, and for the validation cohort. Model ROC area = 0.961 (95% CI: 0.891, 1.0), validation ROC area = 0.936 (95% CI: 0.875, 0.997), reduced model ROC area = 0.90 (95% CI: 0.787, 1.0), and MODS only ROC area = 0.66 (95% CI: 0.50, 0.835).*

Model Validation

The model was validated using an additional cohort of subjects enrolled using the same inclusion and exclusion criteria. Data from 68 additional patients enrolled between May 2005 and March 2006 were used for model validation. One patient was excluded because of lack of TEG data and another patient was excluded because of lack of TNF value resulting in 66 patients available for validation. Demographics for the validation cohort were similar to the model cohort except that the validation group had higher mean % FT ($p = 0.011$) and % second degree burns ($p = 0.04$) compared with the model (Table 1). Three patients had combined burn and nonburn traumatic injuries and were categorized into one of two groups based on their predominant injuries.

Validation was performed using a ROC curve analysis to measure the predictive power of the model computed on the validation cohort. Probability of mortality was calculated for each validation cohort subject using the previously generated model.

The correlation coefficient between the model probability of mortality and actual mortality was 0.541 ($p < 0.001$). The area under the ROC curve for the validation cohort was 0.936 (95% CI: 0.875, 0.997, $p < 0.001$) as shown in figure 1. When the model (95% CI: 0.891, 1.000) and validation (95% CI: 0.875, 0.997) ROC areas were compared, there was no significant difference between the two indicating excellent performance overall, and a good fit between results of two sets. As a clinically useful tool, we chose >50% probability of mortality as a cutoff to see how well the model performed on our validation cohort. The model correctly predicted mortality in 8 of 10 (80%) patients that eventually died (Table 3). Similarly, the model was able to correctly predict survival in 49 of 56 (87%) patients ($\chi^2 = 20.4$, $p < 0.001$). In the validation cohort, our model was compared with Burn_PS and TRISS in burn and nonburn patients, respectively. The area under the ROC curve for the burn patients was 0.867 (95% CI: 0.713, 1.021) using our model and 0.805 (95% CI: 0.575, 1.035) using the Burn_PS Model (Fig. 2A). The area under the ROC curve for the nonburn trauma patients was 0.974 (95% CI: 0.919, 1.029) using our model and 0.805 (95% CI: 0.575, 1.035) using the TRISS Model (Fig. 2B). The improvement in the area of ROC curves using our model was not significantly different from the Burn_PS and TRISS, however.

DISCUSSION

Outcome scoring systems allow comparisons of quality of care by objectifying and standardizing illness severity.

Table 3 Model Prediction of Validation Cohort Using Probability of Mortality >50% as Cut-off

	Predicted Live	Predicted Die	Total
Live	49 (87%)	7 (13%)	56 (100%)
Die	2 (20%)	8 (80%)	10 (100%)

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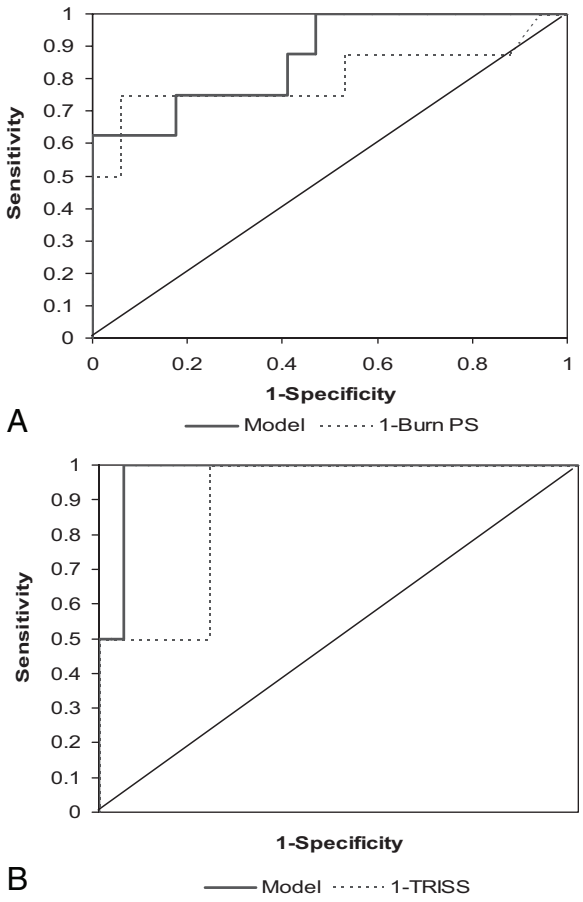

Fig. 2. *The ROC curve for the burn patients was 0.867 (95% CI: 0.713, 1.021) using our model and 0.805 (95% CI: 0.575, 1.035) using the Burn_PS model (*A*). The ROC curve for the nonburn trauma patients was 0.974 (95% CI: 0.919, 1.029) using our model and 0.805 (95% CI: 0.575, 1.035) using the TRISS model (*B*).*

They also facilitate patient stratification in research or treatment protocols and allow a clinician to distinguish the effect of treatment from effect of disease. In this study, our model predicted in-hospital mortality accurately by incorporating the markers of inflammation and coagulation in addition to clinical indices. In particular, TRISS score in trauma patients is often unknown during the early ICU admission because of its dependence on the ISS. Hence, our model has an advantage in allowing early calculation of probability of mortality during the first day of admission in both burn and nonburn trauma patients. The ROC curves for the model and validation cohorts indicate an excellent performance overall, and a good fit between the two sets of subjects.

In the field of nonburn trauma, MOF predictor models have been used as markers of mortality. However, as a result of the variations in the definition of organ failure and the inclusion of medical and surgical patients in many of the published organ failure models, the true incidence of organ failure and resultant mortality has been difficult to establish in the acutely injured population.[20–23] Generally, burned and nonburned trauma patient populations have been analyzed separately and mortality predictor models have focused on one of two injured groups. Inhalation injury, % TBSA, and age are important determinants of survival after burn injury.[24–27] Furthermore, the % TBSA has been proposed as the most important single predictor of mortality.[28] In our study, however, % TBSA fell out and % FT was retained in the regression analysis. The percentage of full-thickness burned wounds was the most important predictor of mortality in our model. This is probably because of our criteria to include patients who were assessed to require 3 or more days of ICU stay rather than including all patients admitted to the Burn ICU as was the case in a previous study by Cancio et al. from this Institute. Hence, our population is skewed toward patients who were assessed to be sicker at the time of ICU admission. Additionally, our model was generated using a prospective observational study database as opposed to being a model generated using a retrospective chart review.

In this study, Marshall's MODS score was incorporated into our mortality model.[4] This score quantifies the severity of the multiple organ dysfunction as an outcome for critical illness. In light of no formal consensus on the definition of MODS, we think that Marshall's score offers an objective physiologic measurement of organ dysfunction in critically ill surgical patients. However, the scoring system is more helpful in predicting mortality when serial measurements are made rather than one time measurement at the time of admission.[29,30] In addition, the scoring system does not include an objective biochemical measure of severity of injury at the time of admission. By incorporating markers of inflammation (TNF) and coagulation (MA), we developed a rigorous prognostic model with reproducible performance. This was evidenced by the exclusion of TNF and MA from the model (Reduced Model), which decreased the ROC area from 0.961 to 0.90 (Fig. 1).

Injury thrusts patients into both the systemic inflammatory response syndrome[31] and an altered coagulation status (hypo and/or hypercoagulable state).[32,33] Elevation of inflammatory cytokines has been documented in the burned and nonburned trauma patient populations. IL-6 and IL-8 have been shown to be elevated early after trauma and are significantly elevated in those who develop multiple organ failure.[34] In burned patients, IL-1 and IL-6 have been shown to be significantly elevated in the plasma of patients when compared with unburned control subjects. IL-1 correlated with burn size and IL-6 correlated with mortality rate.[5] In our patient population, IL-6 and IL-8 levels were significantly elevated in both groups of patients as compared with normal values from healthy controls. However, TNF was the only cytokine that was an independent predictor of outcome in our model.

Via the cytokines, inflammation contributes to the postinjury hypercoagulable state. Of the proinflammatory cytokines, TNF is perhaps one of the best studied because of the use of recombinant human TNF in laboratory and clinical

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investigations. Animals given TNF had reproducible picture of septic shock, cardiovascular collapse, and death.[35,36] In patients with burns, TNF appears to be transiently elevated in response to injury. Based on the studies published by Moreno et al. and Drost et al., TNF is not universally detected during critical illness and is likely secreted in a phasic manner in response to injury.[26,37] TNF is a strong procoagulant by eliciting TF expression on the endothelium and monocytes.[3,12,38] Also, in a dose-dependent fashion, TNF produces a decrease in protein C activation by down regulating the expression of endothelial cell protein C receptor and thrombomodulin, both of which are important in the protein C activation in vivo.[39,40] In relation to mortality, Pellegrini et al. found that the >100 ratio of membrane bound TNF to shedded TNF receptor in blood was found to correlate to Marshall's MODS score and mortality. The study enrolled 25 patients (11 burned and 14 nonburn trauma patients) admitted to the ICU where serial blood was drawn biweekly for monocyte TNF, TNF, and TNF receptors until discharge from the ICU. The first blood sample was drawn up to 48 hours after injury. The ratio and not individual levels correlated to MODS and to less extent to the mortality (5 of 9 false positives).[41] The mortality predictor model in our study incorporated both the MODS score and TNF level early after admission to the ICU and injury. Because of supporting evidence that TNF may be secreted in a phasic manner after injury, its measurement early after injury, as shown in our model, may be more predictive of outcome then its measurement further along a patient's hospital course.

The MA measures the maximal strength of the clot and is the end-product of maximal platelet-fibrin interaction. High MA is indicative of a hypercoagulable state[42] and is an independent contributor of mortality in our model, albeit ranked the lowest of all the predictors. To date, this is a first study utilizing a TEG parameter as an outcome predictor variable in those with burn and nonburn traumatic injuries.

Several limitations of this study need to be addressed. First, this was a single center, prospective study and the model remains to be validated in other medical centers where similar patient populations are managed. Second, it did not take into account patient comorbidities other than age, which may potentially impact the accuracy of this model. Third, the patients in this study had either a burn or nonburn traumatic injury. Only three patients in the validation model had combined injuries. Hence, our model may not be adequate to address the increased morbidity and mortality observed in patients with combined injuries.[43] Finally, the sample size used in generating the model was small.

In conclusion, our mortality predictor model can be used to calculate the probability of death within one day after admission. It incorporates inflammatory and coagulation markers of injury and is applicable to both burned and nonburned trauma patients. After model development, validation of the model was performed. At our Institute, our outcome scoring system has been adopted for patient stratification in the ICU for research protocols.

ACKNOWLEDGMENTS

We deeply thank Nancy Molter, RN, MN, PhD; Elizabeth Frail, RN, BSN; Peggy Bielke, RN, BSN; Kari L. Williams, RN, BSN; and Nik Kypreos for their assistance in this study. We also thank SSG Stanley Rivera in performing the cytokine assays. We appreciate the editorial support of Amy Newland in the preparation of this article. We appreciate support received from the Laboratory Support Branch at the US Army Institute of Surgical Research and the Clinical Investigation Department of the Brooke Army Medical Center.

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